REMARKS

With the entry of the present Amendment, claims 37, 41-49 and 52-59 remain in this application. Claims 37, 39-43 and 59 have been examined; claims 44-58 have been withdrawn. Claims 37, 41, 43, 49, 52 and 59 have been amended to expedite prosecution and to better claim the invention; these amendments are believed to place this application in condition for allowance. None of the amendments made herein constitutes the addition of new matter.

The Rejections under 35 U.S.C. 112, second paragraph

Claims 37 and 39-43 have been rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite. Applicants respectfully traverse this rejection.

Claim 37 is allegedly indefinite in the recitation of "said protein". In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended claim 37 for improved clarity by reciting said **integral membrane** protein.

In view of this amendment, Applicants respectfully submit that these claims are in compliance with the requirements of Section 112, second paragraph.

The Rejections under 35 U.S.C. 112, first paragraph

Claims 37, 42 and 43 have been rejected under 35 U.S.C. 112, first paragraph, as the Specification is allegedly not enabling for all membrane proteins with seven transmembrane segments. Applicants respectfully traverse this rejection.

The Patent Office has acknowledged at page 4 of the Office Action that the Specification has enabled making and using nanoscale particles comprising G protein coupled receptors with the statement "...the specification provides sufficient guidance on how to make and use a nanoscale particle to reconstitute a G-protein coupled receptor

and how to make a nanoscale particle comprising an integral membrane protein comprising an integral membrane protein with a seven transmembrane segment..."

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended claim 37 to recite that the incorporated integral membrane protein is a G protein coupled receptor (GPCR) protein. Accordingly, the withdrawal of the rejection is requested.

The Rejections under 35 U.S.C. 103(a)

Claims 37 and 39-41 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Bayburt et al. (1998) in view of Barnes et al. (1999). Applicants respectfully traverse this rejection.

The cited Bayburt reference is said to teach the reconstitution and imaging of an integral membrane protein (NADPH cytochrome P450 reductase) in a nanometer size phospholipid bilayer stabilized with apolipoprotein A-1. The Patent Office has acknowledged that this reference fails to teach the incorporation of a GPCR such as a 5-hydroxytryptamine (5-HT) receptor. The cited Barnes reference is said to teach the structures and biological functions of 5-HT receptors and a "high level of interest" in the actions of 5-HT and its role in potential therapy, with the Patent Office alleging that it would have been obvious to one of ordinary skill in the art to reconstitute a 5-HT receptor in a nanometer size phospholipid bilayer as taught by Bayburt with a reasonable probability of success.

The present claims encompass artificial membrane scaffold proteins neither taught nor suggested by the cited Bayburt reference, and these claims recite incorporated proteins also neither taught nor suggested by the cited Bayburt reference. Applicants respectfully note that the Bayburt paper describes particles prepared using cytochrome reductase and naturally occurring human apolipoprotein A-1; see also Jonas et al. (1989) J. Biol. Chem. 264:4818-4824, already of record, where it is made clear that the Bayburt

paper relates to apolipoprotein prepared from human plasma. By contrast, the present application relates to artificial membrane scaffold proteins, as described at pages 20 and 26. The artificial membrane scaffold proteins of the present invention are clearly distinguished in structure from the naturally occurring human protein (isolated from plasma). The Specification gives numerous non-limiting examples of the kinds of differences in structure between natural apo A-1 and the artificial membrane scaffold protein variants of the present invention. For example, the Specification describes (artificial) membrane scaffold protein sequences in which certain helices of native apo A-1 are repeated, deleted or replaced with other helices, or have truncations, or have altered hinge regions. See page 14 of the as-filed specification, which describes features of the artificial MSPs. Page 20 also provides information and further refers to mutagenesis and directed evolution of the MSPs. Page 25 discusses properties of the linker sequences, and teachings concerning minimizing linker length and other structural features. The particular primary structures of MSPs taught in the application give rise to better discs than those obtained using natural apo A-1. For example, particle size can be better controlled using these MSPs and the particles are more uniform in size. See page 28, line 20 et seq, where the role of the hinge region in determining particle size is discussed. See also page 4, lines 21 et seq, where there is discussion of certain aspects of size heterogeneity, and page 29, line 1 et seq, for a discourse on removing "half-repeats" so as to reduce size heterogeneity. Bayburt fails to teach or suggest any such structural alterations in natural apo A-1, either individually or any combination of the structural features encompassed by the artificial MSPs of the present invention, and thus, it cannot properly serve as a reference under 35 U.S.C. 103.

Additionally, the cited Bayburt reference teaches cytochrome P450 reductase as the protein incorporated into the particles together with natural apo A-1. It is not a GPCR protein, as recited in the claims as currently amended. The Bayburt reference relates to cytochrome P450 reductase, a tethered membrane protein, as defined in the present Specification (see, e.g., page 2, line 8), the description in the reference notwithstanding. At page 14, beginning at line 25, the as-filed Specification describes tethered membrane

proteins as single pass membrane proteins and also discusses integral membrane proteins, which are specifically exemplified by 7 transmembrane segment proteins such as the GPCRs and bacteriorhodopsin (see the passage beginning at page 18, line 5). An applicant for patent is entitled to be his own lexicographer. Applicants also respectfully refer the Examiner to the definitions of types of membrane proteins in the present application, in the paragraph bridging pages 14 and 15:

> Tethered membrane proteins are composed mostly of a relatively soluble globular domain external to the bilayer and relatively simple (e.g., a single pass helix) which anchors this domain to the membrane bilayer. The globular domain, in nature, can be extracellular or cytoplasmic in orientation. Embedded membrane proteins, as defined herein, are those which include a membrane anchoring segment of the polypeptide, but which also have groupings of hydrophobic amino acids on the surface of the protein, which hydrophobic domains are embedded within the membrane bilayer. Integral membrane proteins are predominantly located within the membrane bilayer; relatively small portions of the protein are exposed to an aqueous environment within the cell or to the extracellular aqueous environment.

By contrast, the GPCRs, identified in the present application as integral membrane proteins, have seven transmembrane domains which are in intimate association with the membrane bilayer (and within the nanoscale discoid particles of the present invention).

There is nothing in either of the cited references that either suggested the combination of artificial membrane scaffold protein and GPCR as currently claimed, and there is nothing in the references that provides any reasonable expectation of success for combining a protein with such complex interaction with a lipid bilayer so that the functional properties of the protein (e.g., ligand binding) would be maintained. (see, for example, In re O'Farrell, 7 U.S.P.Q. 2d 1673, Fed. Cir. 1988). Neither of the cited references provides any reasonable probability of success for the use of the self-assembly into nanoscale disc-like particles by the novel MSPs taught and claimed in the instant application or for the incorporation of proteins with structure and membrane association as complex as those of the 7 transmembrane segment proteins, including the GPCRs. This aspect of traverse also provides a legally sufficient basis for traverse.

Further, Barnes, which describes the 5 HT receptor, does nothing to remedy the failure of Bayburt to teach or suggest structural alterations of the MSP. This failure, on its own, provides a legally sufficient basis to require withdrawal of the rejection. Because neither the Bayburt reference nor the Barnes reference teaches any modification of the apo A-1 primary structure or that positive results could be obtained if modifications in its structure were made, the combination of Bayburt and Barnes cannot properly be found to make obvious claims 37 and 39-41, and therefore the rejection should be withdrawn.

Furthermore, there is nothing in the cited Barnes reference which would motivate one of ordinary skill in the art to combine a 5-HT receptor (or any other GPCR or other 7 transmembrane segment protein) with naturally occurring apolipoprotein A-1 or with any artificial membrane scaffold protein as taught in the present Specification, nor is there any teaching or suggestion in the cited Bayburt reference to incorporate a 5-HT receptor in place of the cytochrome P450 reductase disclosed therein. The courts have cautioned against the impermissible use of hindsight in evaluating patentability (See, e.g., and the necessity that the cited references provide the motivation for their combination. See, for example, ACS Hospital Systems, Inc. v. Montfiore Hospital, Inc., 221 U.S.P.Q. 929, C.A.F.C., 1984; Northern Telecom, Inc. v. Datapoint Corp., 15 U.S.P.Q.2d 1321, 1323 (Fed. Cir. 1990); In re Oetiker, 24 U.S.P.Q.2d 1443 (Fed. Cir. 1992) ("[t]here must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination" and "[t]hat knowledge can not come from the applicant's invention itself."); and In re Dow Chemical Co., 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). This aspect of traverse provides a legally sufficient basis for withdrawal of the rejection under Section 103.

As supported by the as-filed application, the particles claimed are distinct from those described in the cited Bayburt et al. reference, and particles comprising the combination of artificial membrane scaffold proteins and GPCRs are not obvious over the

cited art. In view of the foregoing, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. 103(a).

Claim Objections

Claims 42 and 59 were objected to because they recite nonelected subject matter, i.e., the amino acid sequences set forth in SEQ ID NOS: 6, 9, 19, 23, 29 and 43-45.

The Examiner has recommended that claim 59 be amended to recite "wherein said membrane scaffold protein" for consistency and clarity. Applicants have done so.

With respect to claims related to nanoscale particles and methods related to tethered membrane proteins, claims limited to the use of a tandem repeat membrane scaffold protein variant having the amino acid sequence set forth in SEQ ID NO:17 were identified as allowable. In anticipation of allowability of claims to tandem repeat membrane scaffold proteins and their uses in methods and particles, these claims recite tandem repeat membrane scaffold protein variants of SEQ ID NO:17, amino acids 13 to amino acids 13 to 414 of SEQ ID NO:17, SEQ ID NO:19, amino acids 13 to 422 of SEQ ID NO:19, SEQ ID NO:45 and amino acids 13 to 392 of SEQ ID NO:45. Applicants respectfully request that examination be extended to additional exemplary artificial tandem repeat variant sequences, which are cited in a proper Markush group. The sequences of the MSPs are related in structure and function. Applicants note that the Examiner, in a telephone interview on September 9, 2004, agreed to examine the sequences in claim 60, which have now been incorporated into claim 59, as is appropriate for Markush group practice.

Conclusion

Applicants respectfully submit that the pending claims are in condition for allowance and early notification thereof is requested.

If, in the interest of expediting prosecution, the Examiner has questions or comments, he is invited to telephone the undersigned at the indicated telephone number.

It is believed that the present Amendment does not necessitate the payment of any fees under 37 C.F.R. 1.16-1.17. If this is incorrect, however, please charge any fees pursuant to the foregoing Rules to Deposit Account No. 07-1969.

Respectfully submitted,

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